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(54) Title: METHODS OF DRY POWDER INHALATION

(57) Abstract

A method for inhalation of a dry powder drug includes the steps of providing a dry powder drug composition having a drug particle size of from about 1-7 microns and a mass median aerodynamic diameter of the delivered aerosol of from about 3.5 to 5.5 microns. This composition is loaded into an inhaler which is generally flow rate independent, and with the inhaler having an inspiration flow resistance of about .12 to .21 $(cmH_2O)^{1/2}$ over the range of about 15-60 L/min. The patient inhales the drug composition from the inhaler with an inspiration flow rate of about 15-60 L/min, resulting in a delivery efficiency measured by respirable fraction greater than 20 %.

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DESCRIPTION

Methods of Dry Powder Inhalation

State-of-the-Art

Considerable information regarding the in-vitro and in viv-performance of metered dose inhalers and dry powder inhalers has been reported in literature. In general, metered dose inhalers are inhalation flow rate independent, but require significant coordination and even then will deliver only about 20% of the nominal does to the lungs. Radiolabelled deposition studies of metered dose inhalers typically demonstrate the usual 3 micron particles deposit mainly in the more central airways. Recently, 3M Corporation, Minneapolis, MN, USA, has presented data that indicates that if the particle size could be reduced to a mass median aerodynamic diameter (MMAD) of 1.5 microns an increase in the total amount of particles and peripheral deposition could result. This result appears to confirm the more uniform belief that smaller particles are required to maximize peripheral deposition (i.e. particles in the 1-2 microns size range).

Now in the case of dry powder inhalers, most studies have shown the major issue surrounding dry powder delivery is related to the flow rate dependence. The performance of the dry powder inhalers now in use vary significantly with inhalation flow rates ranging from 15 to 120 liters/min inspiratory effort. In general, at least 60 liters/min inspiratory flow has been required to consistently deaggregate a dry powder sufficiently to result in particles which could be inhaled. For some

products, inhalation flow rates significantly greater than 60 L/min are required before sufficient deaggregation can occur. Both the total amount of drug formulation delivered to the patient as well as the aerodynamic particle size are affected by increasing the inhalation flow rate. For example, at 30 L/min, aerodynamic sizes of the active particles may be as large as 8 to 10 microns but above 60 L/min the same metered dose inhaler formulation may be 2-4 microns. In addition, the dose-to-dose variation may be significantly greater as the flow rate is decreased.

Unfortunately, requiring the patient to breathe forcefully when using a metered dose inhaler is in direct opposition to maximizing deposition. Traditional thinking is that 30 L/min is a well controlled inhalation flow rate. And, currently no data has been presented which shows that using existing metered dose inhaler technology, significant uniform and peripheral particle deposition had occurred, at any flow rate.

Finally, it is now generally believed that for a protein to be efficiently delivered systemically through the lungs, a very small particle size is required to facilitate peripheral deposition, preferably in the alveoli. The size often considered necessary for this purpose is in the range of one micron.

Statement of the Invention

Utilizing the dry powder inhalation system described in PCT/US93/09751, published 28 April 1994, and incorporated by reference (referred to here as the SPIROS

system), the following in vitro and in vivo observations have been made:

1. The in vitro delivery of several drug/lactose blends has been shown to be flow rate independent over a range flow rates from 15 to 60 L/min. Both the size of the active particles and the amount of drug delivered were independent of flow rate.

2. Utilizing a radiolabelled technique, the flow rate independence of the delivery system was confirmed in vivo (15 to 60 L/min). In addition, this study clearly indicated that even with a slow inhalation rate (less than 60 L/min), the drug was delivered uniformly throughout the lung, including the periphery. In fact, there is a tendency to have higher peripheral lung deposition at the low flow rate.

3. In the metered does inhaler studies, where the in vitro determined MMAD is between 2 to 3 microns, in vivo deposition is typically quoted as between 10 to 20% of the nominal dose. Deposition of albuterol from the Spiros system was shown to be equal to or better than what is expected from metered dose inhalers, even though the aerodynamic particle size of the active particle was approximately 4.5 microns.

4. Recent pharmacokinetic (blood level) data from a comparison of beclomethasone delivered from a metered dose inhaler compared to Spiros, indicated that twice as much drug was delivered to the lung from the Spiros system. Again, the particle size of the active particle in the dry powder inhaler system was between 4 to 5 microns, while the metered dose inhaler formulation was between 3 to 4 microns.

5. Using calcitonin as a model peptide for systemic delivery, the bioactivity following dosing with the Spiros system has been estimated to be greater than 20% compared to a subcutaneous injection. In contrast, an approved nasal product has only 3% bioavailability. Surprisingly, the particle size of the calcitonin from the calcitonin/lactose blend was 4-5 microns, yet excellent systemic availability was achieved (>20%).

Using the above observations, the following conclusions regarding dry powder delivery can now be made.

Until a dry powder inhaler was developed which adequately deaggregated the powder at low inspiratory flow rates, it was not possible to separate out the performance of the dry powder inhaler from the patient inhalation maneuver. Thus, the relationship between particle size and deposition was confused with the performance of the dry powder inhaler itself. With the development of the Spiros system, we have now demonstrated that under low flow rate conditions, particle sizes which would be considered on the upper end of achieving good lung deposition can actually provide deposition uniformly throughout the respiratory tract.

Importantly, the delivery of the dry powder from the Spiros system is no longer degraded by the patient's inhalation flow rate, as is the case with existing dry powder inhalers. Slow deep inspiration is key to the increased drug delivery and peripheral deposition. Thus, the delivery system must efficiently operate under these conditions. With the deagglomerating dry powder at low inhalation flow, surprising good results were obtained

over what could be expected for commercially available metered dose inhalers or dry powder inhalers.

The results which were obtained in vivo were possible because 1) Spiros is inhalation flow rate independent, and 2) Spiros efficiently deaggregates the powder. Therefore, patients were able to be trained and benefit from the slow deep inhalation maneuver. The slow deep inhalation permits more of the particles to navigate past the throat (and not be collected by impaction) and be available to deposit in the lung. Secondly, the slow deep inhalation maneuver fully dilates the lungs, driving the particles further into the lung, and inhibits premature impaction of the larger particles in the upper airways.

To facilitate the slow inhalation, some device resistance is required. If no resistance is encountered, then it is difficult for a patient to inhale slowly. This is what is often observed for metered dose inhalers and some dry powder inhalers such as Rotohaler and Spinhaler. If flow resistance is too high, patient discomfort results when the inhaler is used at the optional flow rate. It can also result in higher air velocity in passageways. This increase in velocity increases upper airway deposition by impaction. Less deposited drug is then available to the lower regions of the lung. The drug may be a systemic or topical drug for treating asthma. The drug may be a protein, a polypeptide or a hormone, for treating lung or other conditions.

Detailed Description

1. A dry powder inhalation system consisting of micronized drug in the 1 to 7 micron range, alone or in blends of lactose or some other suitable inert carrier (i.e., sugars, salts).

2. The inhalation system should be flow rate independent over the range of interest, i.e., 10 or 15 - 60 L/min.

3. The mass median aerodynamic diameter (MMAD) of the delivered aerosol (Cascade impactor 26.3 L/min, UPS throat) should be 3.5 - 7 and preferably 3 - 6 microns. Additionally, the respirable fraction (fraction of particles penetrating the impactor inlet with a particle size less than 5.8 microns) should be greater than 20%. The most preferred level would be greater than 30 to 40%. This describes the efficiency of the device to deagglomerate the powder. A device such as the Beclomethasone Rotohaler which could be considered flow rate independent over this range delivers an aerosol of 10 microns and a respirable fraction of 2.6%.

The device resistance (slope of the flow vs. pressure drop curve (in units of (cm $H_2O^{1/2}$)) should be .12 to .21 with a most preferred range of 0.12 to 0.18.

Claims:

1. A method for inhalation of a dry powder drug, comprising the steps of:

a) providing a dry powder drug composition having a drug particle size of from about 1-7 microns and mass median aerodynamic diameter of the delivered aerosol of from about 3 to 6 microns;

b) loading the dry powder drug composition into an inhaler which is generally flow rate independent, and with the inhaler having an inspiration flow resistance of about .12 to .21 (cm $H_2O)^{½}$) over the range of about 10-60 L/min;

c) inhaling the drug composition from the inhaler with an inspiration flow rate of about 15-60 L/min, resulting in a delivery efficiency measured by respirable fraction of at least 20%.

2. The method of claim 1 wherein the drug composition includes active particles and the aerodynamic particle size of the active particles is about 4.5 microns.

3. The method of claim 1 wherein the drug comprises a systemic or a topical drug for treating asthma.

4. The method of claim 1 wherein the drug comprises a protein, a polypeptide, or a hormone.

5. The method of claim 1 wherein the percent of particles greater than 5 microns is about 30-90.

6. The method of claim 1 wherein the inhaler has a flow resistance of from about .12 to .18 (cm H_2O)$^{\frac{1}{2}}$.

7. The method of claim 1 wherein the drug composition includes an inert carrier.

8. The method of claim 1 wherein the drug comprises beclamethasone.

9. The method of claim 1 wherein the respirable fraction (fraction of particles penetrating the inpactor inlet with a particle size less than about 5.8 microns) is at least 20%.

10. The method of claim 1 wherein the flow resistance is about .12 to .21 (cmH_2O)$^{\frac{1}{2}}$ over the range of 15-60 L/min.

11. The method of claim 1 wherein the mass median aerodynamic diameter of the delivered aerosol is from about 3.5 to 5.5 microns.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61K 9/12
US CL :424/45; 128/203.12
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 424/45; 128/203.12

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,681,752 A (MELILLO) 21 July 1987, see entire document.	1-11
Y	US 4,810,488 A (JINKS) 07 March 1989, see entire document.	1-11
Y, P	US 5,524,613 A (HABER et al.) 11 June 1996, see entire document.	1-11

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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